

### **Influenza vaccination and prevention of cardiovascular disease mortality**

Catharine Paules and Kanta Subbarao presented in their Seminar (Aug 12, 2017, p 697) the clinical features, therapeutic options, and controversies regarding treatment and prevention of seasonal influenza infection.<sup>1</sup> Although they acknowledged that influenza can impair different organ systems, little attention was given to cardiovascular

consequences. Ischaemic heart disease is the leading cause of death worldwide and influenza vaccination could reduce cardiovascular mortality, particularly in patients with coronary heart disease for whom cardiovascular mortality risk has been reported to be halved by influenza vaccination.<sup>2</sup> Although this conclusion relies on moderate-quality randomised placebo-controlled trials enrolling a small number of patients followed up for up to 1 year,<sup>2</sup> the possible reduction of cardiovascular disease burden in patients with coronary heart disease is huge.

In Europe, which has an influenza vaccination coverage of 45.6%,<sup>3</sup> about 30 million individuals have ischaemic heart disease,<sup>4</sup> and more than half a million of these people will die from cardiovascular causes (figures based on the conservative standardised mortality rates of individuals aged 65 years and older<sup>5</sup>). Considering that influenza vaccination is associated with a 24% risk reduction of cardiovascular mortality in this population (the lower limit of 95% CI of the estimate),<sup>4</sup> an increase of coverage to 75% (as recommended by the European Council<sup>3</sup>) would translate to about 42 000 potentially avoidable cardiovascular deaths in Europe among individuals with ischaemic heart disease.

We think that highlighting this potential effect on ischaemic heart disease is important, since this disease is responsible for 12.8% of total disability-adjusted life-years lost in Europe,<sup>3</sup> and thus is relevant for all stakeholders in health-care decision making.

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### Authors' reply

We thank Daniel Caldeira, Joaquim J Ferreira, and João Costa for highlighting the effect of influenza infection on underlying cardiovascular disease and the role of influenza vaccination in potentially mitigating this risk. Although we briefly mentioned that influenza infection could exacerbate underlying cardiovascular disease in our Seminar,<sup>1</sup> we were unable to fully expand on this point because of word-count restrictions. In this regard, an epidemiological link between influenza and excess deaths associated with cardiovascular disease was suggested as early as in the 1930s.<sup>2</sup> Since then, several observational studies have supported an association between influenza infection, influenza-like illness, or respiratory tract infections and poor outcomes associated with underlying cardiovascular disease. In particular, a strong association with an increased risk of acute myocardial infarction has been reported.<sup>2,3</sup> Therefore, influenza vaccination could potentially prevent cardiovascular events; a Cochrane review evaluated evidence for this intervention.<sup>4</sup> The systematic analysis revealed that in randomised controlled trials that examined influenza vaccination as a mechanism of secondary prevention, significantly fewer cardiovascular deaths occurred in the vaccine group

than in the control group (risk ratio 0.45, 95% CI 0.26–0.76;  $p=0.003$ ). However, a difference was not observed for specific cardiovascular events such as acute myocardial infarction, and the effectiveness of influenza vaccination in primary prevention could not be assessed from available data.

The findings from the Cochrane review had moderate bias because sample sizes were small and cardiovascular events were rare. However, the findings support influenza vaccination in individuals with cardiovascular disease, and are reflected in the recommendations for influenza vaccination from the US Centers for Disease Control and Prevention<sup>5</sup> and the European Centre for Disease Prevention and Control.<sup>6</sup> As stated by Caldeira and colleagues in their Correspondence, cardiovascular disease is a leading cause of death and disability worldwide. Mitigating the risk of influenza infection in this high-risk group through interventions such as vaccination could have a substantial positive effect on public health. More studies are needed to fully understand the association between influenza infection and cardiovascular events and the role of influenza vaccination as a prevention strategy.

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